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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,029	06/09/2006	Gabriela Chiosis	MSK.P-072	1546

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EXAMINER	
KOSSON, ROSANNE	
ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
03/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,029	CHIOSIS ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *18-31,39 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,32-38,41 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on February 7, 2008 has been received and entered. Claims 3, 7 and 32 have been amended. No claims have been canceled. Claims 41-42 have been added. Claims 18-31, 39 and 40 were withdrawn in a previous Office action as being drawn to non-elected inventions. Accordingly, claims 1-17, 32-38, 41 and 42 are examined on the merits herewith.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

In view of Applicants' amendment to claim 7, the objection is withdrawn.

Claim Rejections - 35 USC § 112

In view of Applicants' amendment to claim 32, the rejection of claim 32 is withdrawn.

Claim 6 is again rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 6 recites that the different cell types have at least partially different Hsp90-dependent activity, which renders the meaning of the claim unclear. The Hsp90-dependent activity of two types of cells is either the same or different. It cannot be partially different or at least partially different. Moreover, the activities of the two cell types must be different for the assay to work and distinguish between the two (otherwise it is of no use to use more than one cell type). Appropriate correction is required. The words "at least partially" may be deleted. This rejection was discussed in the previous Office action.

Applicants assert that " at least partially different Hsp90-dependent activity" means a change in the expression level of some proteins but not all proteins. This statement does not clarify the claim, because neither Applicants nor the specification describes which proteins have the same level of expression and which proteins have a different level of expression in the different cell types used in the claimed method. Thus, in performing the claimed method, one of skill in the art would not know which cell types (at least two different cell types) to select for the assay or which protein expression levels to check or measure to determine whether two or more particular cell types would be suitable for the claimed method as having somewhat different, but not completely different, patterns of protein expression. It is also not clear how different the protein expression patterns have to be so that the assay results with a first type of cell will be different than the assay results with a second type of cell (or additional types of cells), in order for the assay to distinguish between or among cell types. It is two (or more) different Hsp90-dependent activities in the form of two (or more) different patterns of Hsp90-dependent protein expression that allows one to distinguish between two (or among more) different cell types used in the claimed assay. In view of the foregoing, the rejection of record is maintained.

Claim Rejections - 35 USC § 103

Claims 1-17 and 32-38 are again rejected, and claims 41-42 are rejected, under 35 U.S.C. 103(a) as being unpatentable over Gewirth et al. (US 2002/0160496 A1) in view of Rosen et al. (WO 02/094196 A2); Chiosis et al. ("A small molecule designed to bind to the adenine nucleotide pocket of Hsp90 causes Her2 degradation and the growth arrest and differentiation of breast cancer cells," Chem & Biol 8:289-299, 2001; Devlin et al. (US 6,060,598); Bennett et al. (US 4,902,630); and Pagé et al. (US 5,981,564). This rejection was discussed in the previous Office action.

Applicants assert that elements of the claims were left out in the rejection because, the first assay, a reduction in the polarization of the fluorescent label is measured, not a reduction in fluorescence. In reply, as previously discussed, the rejection is one of obviousness, not anticipation. The advantages of using a label that emits polarized fluorescence, rather than any fluorescent dye, are disclosed by Devlin et al. To reiterate, Devlin et al. disclose that assays with a fluorescent label in which bound label need not be separated from free label before measurement because the signals of the bound label and free label are different (homogeneous labeling) suffer from the disadvantages that they are not sensitive and have a high background (see col. 3, lines 49-56, and col. 4, lines 53-67). Labels like fluorescein, however, emit polarized light and can be exploited in assays with a fluorescein-labeled compound, such as a drug, to determine the presence or amount of the drug (see col. 5, line 29, to col. 6, line 14). Fluorescein labels may be used in fluorescence polarization assays. Fluorescence polarization assays have the advantages of homogeneous assays (simpler, fewer steps, no need to separate unbound label) and the advantage that they are not dependent on light intensity, fluctuations in which typically cause assay variability (see col. 6, lines 39-54). Also, the degree of polarization of the labeled compound is proportional to the sensitivity of the assay (see col. 17, lines 28-31). As a result, selection of a highly polarizing label yields an assay with improved sensitivity compared to other fluorescence assays. Bennett et al. disclose that fluorescence polarization assays may also be performed in which the polarizing fluorescent label is bound to a relatively large molecule such as protein (see col. 3, lines 41-49; col. 4, lines 22-36; and col. 7, lines 16-34). Prior to Bennett et al., it had been thought that such assays would work only when the label was bound to a relatively small molecule (see col. 2, lines 49-63). Bennett et al. disclose several examples of fluorescent labels that emit polarized light when bound, e.g., FITC (fluorescein isothiocyanate) (see col. 1, line 50, to col. 2, line 2). Pagé et al. disclose that FITC

and BODIPY are functional equivalents in that both are fluorescent labels that may be used in fluorescence polarization assays (see col. 20, lines 20-34). As the prior art teaches the advantages of fluorescence polarization assays, claim elements have not been omitted from the rejection. As previously discussed, it would have been obvious to one of ordinary skill in the art at the time of the invention to use an improved label, such as FITC or BODIPY, in the method of claim 1, and its dependent claims, because the prior art teaches the advantages of labels that emit polarized fluorescent light.

Applicants assert that Bennett et al. are irrelevant, because Applicants use a small ligand that binds to Hsp90 in their assay, not a large protein. In reply, this feature is not a claim limitation in most of the claims; no structural features of the ligand are recited. Only claims 9 and 36-38 recite one ligand, geldanamycin. In view of the teachings of this reference, the advantages of fluorescence polarization assays and labels that emit polarized fluorescent light, such as FITC, the reference is relevant.

Regarding Gewirth et al., Applicants assert that the label used by Gewirth et al., 8-ANS, binds inside a pocket of Hsp-90 and that one of skill in the art would not be able to predict how FITC and BODIPY bind to Hsp-90. Applicants assert that it would be impractical to predict the usefulness of a fluorescence polarization assay and that, if Hsp-90 undergoes a conformational change when a ligand is bound, it may become more difficult to exchange binding species in and out of the binding site, lengthening the time required to perform the assay, which is a disadvantage. In reply, the method of claims 1, 2, 9-17, 32-38 and 41 and 42 (claim 1 and its dependent claims related to the first assay) is recited broadly. These claims recite a method of screening for molecules that inhibit the binding of Hsp-90 to an Hsp-90 ligand. The ligand is tagged with a label that emits a different signal in the bound state than in the free (unbound) state, so that one can determine whether or not the test molecule (or candidate molecule)

disrupts the binding of Hsp-90 and its ligand. As a result of the language used in the claims, the ligand need not have the same binding site as 8-ANS. As for predicting the binding of FITC or BODIPY to Hsp-90, the two labels are known, conventional labels, not Applicants' invention, and one of ordinary skill in the art at the time of the invention would have expected a known Hsp-90 ligand tagged with a known label to bind to Hsp-90 is such a way that the signal from the bound ligand would have been detectable. As discussed previously and above, the usefulness of a fluorescence polarization assay is known in the art. In the claimed method, as noted above, one measures whether or not a test molecule disrupts the binding of Hsp-90 and its ligand. Exchanging binding species in and out of the binding site (or 8-ANS binding site) is not required, and, consequently, extra time needed for this exchange is also not required.

Regarding claim 2, this claim was examined with claim 1 and is not considered to be separately patentable, because claims 1 and 2 are drawn to an in vitro protein-based assay to screen for inhibitors of the binding between Hsp-90 and one of its ligands. It was conventional at the time of the invention (and still is) to use a cell lysate to study a protein expressed by a particular cell in an in vitro biochemical assay that is not cell-based. Claim 2 does not recite how crude the lysate is or whether or not it was purified to any degree. It was conventional at the time of the invention to remove insoluble material, such as cell membranes, from a cell lysate before using the lysate in an assay, for reasons that would have been apparent to one of ordinary skill in the art (e.g., for accuracy in measuring volumes, protein concentrations, analyte concentrations, etc. and for removing interfering substances). If Applicants' point is that their assay works when lysates from which no membranes have been removed are used, this limitation may be added to the claims.

Regarding claim 9, this claim recites that the ligand that binds to Hsp-90 is geldanamycin that has a label at the position of C-17. As previously discussed, Rosen et al. disclose that

geldanamycin, 17-AAG and other compounds are ligands for Hsp-90 (see pp. 3-4). 17-AAG stands for 17-(allylamino)-17-demethoxygeldanamycin, a geldanamycin derivatized with a reactive functional group at the C-17 position that allows for the attachment of a label. Rosen et al. disclose that their ansamycin Hsp-90 ligands are well known in the art (see p. 6, third paragraph). Thus, Rosen et al. disclose a suitable ligand for the assay of Gewirth et al., a ligand that Applicants recite in claim 9.

Regarding claim 17, Examiner's point was that the claimed method measures the amount of polarized fluorescence in the absence of a test compound (as a control) and the decrease in the amount of polarized fluorescence as the indicator that a test molecule disrupts the binding between Hsp-90 and one of its ligands. Thus, for the claimed assay to work, in the control and in the test samples, enough ligand must be present to saturate the ligand binding sites, a portion or region of Hsp90 being a ligand binding site. If the amount of polarized fluorescence measured depends on multiple factors, such as Hsp-90 concentration (and/or degree of binding site saturation by the ligand, disruption of Hsp-90–ligand binding, ligand concentration, etc.), one would have no idea what is being measured during the assay or what is occurring during the assay. The assay result would be meaningless. If Examiner has misinterpreted the meaning of the claim, Applicants are invited to explain the meaning.

Regarding claims 41 and 42, DTT is a conventional laboratory reducing agent that is added to a biological preparation, such as a cell preparation or cell lysate to inhibit oxidation of the molecules in the preparation. Gewirth et al. disclose that DTT is added to their buffers used in purifying recombinant Hsp-90 proteins (see paragraphs 111 and 113) and in purifying Hsp-90 proteins from cell lysates (see paragraph 475). DTT is also added to their assay buffer in an assay to test the effect of various inhibitors on the binding of GRP94 (which is an Hsp-90 protein) to one of its labeled ligands, labeled NECA (NECA is N-ethylcarboxamidoadenosine)

(see paragraphs 2 and 477). As a result, the addition of DTT to the assay buffer in the method of claims 1 or 2 does not distinguish Applicants' invention over the prior art, as the use of DTT to maintain the integrity of a protein is routine in the art. Also, it would have been obvious to one of ordinary skill in the art at the time of the invention to add DTT to the buffer used in a screening assay to study inhibitors of Hsp90–ligand binding, because Gewirth et al. disclose adding DTT to such a buffer.

In view of the foregoing, the rejection of record is maintained.

No claim is allowed.

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is (571)272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Nashaat Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rosanne Kosson
Examiner, Art Unit 1652

/Elizabeth Slobodyansky, PhD/
Primary Examiner, Art Unit 1652

rk/2008-02-20